Subject: Clinical review of Supplement to license application for Infanrix® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine, Adsorbed) to include fifth dose indication

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To: STN 103647

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2.0 General Information

Product Name: Infanrix® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine, Adsorbed)

U.S. License #: 1090

STN #: 103647

Sponsor: GlaxoSmithKline (GSK)

Manufacturer: SmithKline Beecham Biologicals (SKB)

Proposed Indication: In 1997, Infanrix® was licensed for the first four doses of the recommended five-dose series of Diphtheria and Tetanus Toxoids and Acellular Pertussis (DTaP) vaccine. The following indications were requested in this Supplement:

- Fifth dose of DTaP vaccine in children ages 4-6 years who previously received four doses of Infanrix®
- Fourth or fifth dose of DTaP vaccine, following three or four doses, respectively, of any DTaP vaccine

Dosage Form: Liquid, single dose vials or pre-filled syringes

Adjuvant: Aluminum hydroxide

Preservative: 2-phenoxyethanol

Route of Administration: Intramuscular

Product/Formulation (per dose):

- Inactivated pertussis toxin (PT) 25 µg
- Filamentous hemagglutinin (FHA) 25 µg
- Pertactin 8 µg
- Diphtheria toxoid 25 Lf
- Tetanus toxoid 10 Lf
- Aluminum ----------, <0.625 mg of aluminum
- 2-phenoxyethanol 2.5 mg
- NaCl, 4.5 mg
- Formaldehyde, ≤100 µg
- Polysorbate 80 (Tween 80), ≤100 µg

Related Products:

- Pediarix [Diphtheria and Tetanus Toxoids and Acellular Pertussis, Hepatitis B (Recombinant), Inactivated Poliovirus Vaccine Combined] (IND ------); BLA STN #103907 approved December 2002)
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2.1 Regulatory Review

A summary of the review process is presented in Table 1. [---
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---] In August 2000, the sponsor --------- submitted a Supplement to the Infanrix® license application to include a fifth dose indication (STN 103647/5001). This supplement contained additional immunogenicity data and the same safety data that had been included ---
---. In January 2001, CBER issued a complete response letter that included requests for additional analyses. The sponsor responded in July 2002. In the response, the sponsor noted that for some subjects enrolled in the two pivotal German clinical studies, study information had been recorded on German worksheets that had not been taken into account in preparation of the databases used for the August 2000 supplement. These worksheets had been designed for recording information on local reactions associated with commercial vaccines administered outside of the study. Consistency checks of data from the worksheets with the previously existing databases resulted in changes to the safety databases and revisions of the adverse events tables that were included in the original study reports. In January 2003, CBER issued a complete response letter, requesting additional analyses using the revised safety databases. The sponsor submitted a response to this letter in February 2003.

Table 1. Chronology of regulatory review

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Supplement submitted by sponsor	August 2000
CBER complete review letter	January 2001
Sponsor submission of response to CBER review	July 2002
CBER complete review letter	January 2003
Sponsor submission of response to CBER review	February 2003

2.2 Material Reviewed

I have been assigned review of the safety data contained in this Supplement. I have reviewed the safety information in the following volumes:
STN 103647/5001 (August 2000) Volumes 1-6
STN 103647/5001.5001 (July 2002) Volumes 1-5
STN 1036475001.5003 (January 2003) Volume 1
STN 103647/5001.5004 (February 2003) Volume 1
STN 103647/5001.5006 (May 2003) Volume 1

Review of the clinical immunogenicity data has been assigned to another reviewer.

3.0 Background

The routine diphtheria, tetanus, and pertussis vaccination schedule for children less than seven years of age in the United States comprises five doses of DTaP vaccine. The first three doses are generally administered at 2, 4, and 6 months of age, followed by a fourth dose at 15-18 months of age and a fifth dose at 4-6 years of age.

In the U.S., between 1996 and 2002, five DTaP vaccines from different manufacturers were approved for use in infants following demonstration of efficacy against pertussis in clinical trials. Currently, three of these vaccines [Infanrix®, Tripedia® (Aventis Pasteur Inc), and Daptacel™ (Aventis Pasteur Ltd)] are being manufactured and are available for use. Of the five DTaP vaccines that have been approved for use in infants, two vaccines, *ACEL-IMMUNE* (Lederle Laboratories) and Tripedia®, have been approved for all five consecutive doses of the DTaP series. Approval of the fifth dose of these vaccines following four previous doses of the same vaccine was based on an evaluation of safety; immunogenicity data were not required. [----------
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In 1997, Infanrix® was licensed in the U.S. for use in infants and children six weeks to seven years of age (prior to the seventh birthday) for the first four doses of the DTaP series. At that time, insufficient data were available on the safety of a fifth consecutive dose of Infanrix®.

In previous studies in which subjects received four consecutive doses of Infanrix®, the incidence of fever and local injection site reactions (erythema, swelling, pain) increased with successive doses. The severity of local injection site reactions also tended to increase with successive doses. Extensive swelling of the injected thigh was reported spontaneously in 1.2% of 5,361 subjects who received a fourth consecutive dose of Infanrix® in a German study. In a subset of 1,809 children from this study for whom standardized adverse events diaries were available, extensive swelling of the injected thigh was spontaneously reported in 2.5%. An increase in frequency of local reactions with successive doses, as well as extensive swelling reactions following the fourth and fifth consecutive doses, have also been reported for DTaP vaccines from other manufacturers.

4.0 Description of Clinical Data Sources
This supplement contains clinical data from two studies conducted in Germany (Studies APV-118 and APV-120) and one U.S. study [Multicenter Acellular Pertussis Trial (MAPT)], that evaluated the safety of a fifth consecutive dose of Infanrix®.

The supplement contains no data on use of Infanrix® following three or four doses of a U.S.-licensed DTaP vaccine from a different manufacturer. The supplement contains data on 23 subjects who received Infanrix® following four doses of another DTaP vaccine manufactured by SKB, but that is not licensed in the U.S.

Table 2. Number of subjects who received a fifth consecutive dose of Infanrix® in clinical studies and who were included in the analyses of safety

Study	N
APV-118	93
APV-120	390[1]
MAPT	22
Total	505

[1]Safety data were available on 2 additional subjects who were excluded from the analyses because of underlying serious chronic diseases that could have affected the assessments of safety.

5.0 Multicenter Acellular Pertussis Trial (MAPT): The Supplement contains published reports from this study. Neither the study protocol or a study report was submitted. Briefly, healthy 4- to 6- year old children were enrolled at five NIAID Vaccine Treatment and Evaluation Units to receive a fifth dose of DTaP or whole-cell DTP vaccine. All had been randomly assigned to receive 3 doses of DTaP or whole-cell DTP vaccine at 2, 4, and 6 months of age and a fourth dose at 15-20 months of age as part of earlier National Institutes of Health vaccine trials. Parents recorded the occurrence and magnitude of fever, irritability, and injection site redness, swelling, and pain for 3 days after vaccination. In the earlier trials, 120 infants had received 3 doses of Infanrix® at 2, 4, and 6 months of age, including 76 who received a fourth consecutive dose of Infanrix® at 15-20 months of age. In the fifth dose study, 22 children ages 4-6 years received a fifth consecutive dose of Infanrix®. Data on solicited adverse events for these 22 children are presented in the table below.

Table 3. MAPT: Frequency of solicited adverse events within the 3 days following the fifth consecutive dose of Infanrix® among 22 children ages 4-6 years

Adverse event	%
Fever[*]	
≥100.1°F	4.6
≥101.1°F	4.6
>102°F	4.6
Irritability[¦]	
any	22.7
moderate or severe	0
severe	0
Redness	
any	59.1
>20 mm	40.9
>50 mm	36.4
Swelling	
any	50.0
>20 mm	45.5
>50 mm	27.3
Pain[¶]	
any	54.6
moderate or severe	27.3
severe	4.6

[*] oral temperature

[¦] moderate irritability: prolonged crying and refused to play; severe irritability: persistent crying and could not be comforted

[¶] moderate pain: cried or protested to touch; severe pain: cried when arm moved

source: Pichichero ME, Edwards KM, Anderson EL, et al. Safety and immunogenicity of six acellular pertussis vaccines and one whole-cell pertussis vaccine given as a fifth dose in four- to six-year-old children. *Pediatrics* 2000;105(1):e11.

6.0 Study APV-118: Randomised, blinded clinical study to assess the immunogenicity and reactogenicity of SKB's dTpa and DTPa vaccines and a commercial Td vaccine administered as a booster dose to healthy children 4 to 6 years old, previously vaccinated with four doses of SKB's DTPa vaccine in the first two years of life.

6.1 Safety Objectives pertaining to Infanrix®

Primary: there were no primary objectives pertaining to safety

Secondary: To assess and compare the reactogenicity of the study vaccines

6.2 Design: Randomized, single (subject) blinded comparative study with three groups: dTpa, Infanrix®, and Td (2:1:1 randomization scheme). Subjects in the Td group were not informed of the identity of the vaccine given until one month later, at which time they were randomized (1:1) to receive one of two acellular pertussis vaccines: Pac Merieux or pa (see Table 4 below for description of vaccines). Members of the study staff, including those who administered vaccines and those who evaluated adverse events, were not blinded to which vaccine was given.

6.3 Protocol

Study Period: January 3, 1998 - May 19, 1998

Study population: The study was conducted at 8 sites in Germany.

Inclusion criteria

- healthy child between 4 and 6 years of age
- written informed consent obtained from the parents/guardians
- vaccinated with four doses of Infanrix® in the first two years of life in Studies APV-039* and APV-039B*

*In Study APV-039 subjects received Infanrix® at 3, 4, and 5 months of age. These children were eligible to receive a fourth dose of Infanrix® in Study APV-039B at 10-36 months of age (the mean age at vaccination was 20 months). Of 22,505 children who received the first three doses of Infanrix® in Study APV-039, 5,361 received a fourth dose of Infanrix® in Study APV-039B.

Exclusion criteria

- history of a fifth dose of diphtheria, tetanus and/or pertussis vaccine
- history of diphtheria, tetanus and/or pertussis disease
- known hypersensitivity to any component of the vaccine
- history of allergic disease or reactions likely to be exacerbated by any vaccine component
- major congenital defects or serious chronic illness
- history of progressive neurological disease
- immunosuppressive therapy (with the exception of topical corticosteroids)
- any suspected or confirmed immune disorder (including HIV infection)
- administration of immunoglobulins and/or any blood products within the three months preceding vaccination or planned administration/ administration during the study period
- acute febrile illness ($\geq$37.5^{o}C, axillary or oral) at time of planned vaccination
- use of any investigational or non-registered drug or vaccine other than the study vaccines during the study period or within 30 days/5 half lives (whichever is longer) preceding vaccination
- planned administration/ administration of a vaccine not foreseen by the study protocol during the period starting from 30 days before vaccination and ending 30 days after
- absolute contraindications or precautions for an additional DTaP vaccine dose:
    - hypersensitivity reaction to the vaccine
    - encephalopathy within 7 days of vaccination
    - fever $\geq$40.5^{o}C (rectal temperature; $\geq$40.0^{o}C axillary) within 48 hours of vaccination not due to another identifiable cause
    - collapse or shock like state (hypotonic hyporesponsive episode) within 48 hours of vaccination
    - seizures with or without fever within 3 days of vaccination
    - persistent, inconsolable screaming or crying for $\geq$3 hours, within 48 hours of vaccination

Study vaccines

Table 4. Study APV-118—Composition of study vaccines

Vaccine	PT µg/dose	FHA µg/dose	PRN µg/dose	Diphtheria toxoid	Tetanus toxoid
dTpa*	8	8	2.5	2.5 Lf	5 Lf
Infanrix®	25	25	8	25 Lf	10 Lf
Td-pur[+]				1.5 Lf	10 Lf
pa*	8	8	2.5		
Pac Merieux[#]	23.4	23.4			

*manufactured by SKB; not licensed in the U.S.
[+]manufactured by Chiron-Behring; licensed in Germany; not licensed in the U.S.
[#]manufactured by Pasteur Merieux; licensed in Germany; not licensed in the U.S.

Vaccination Schedule: Subjects assigned to receive either dTpa or Infanrix® received one dose of the assigned vaccine. Subjects assigned to receive Td received one dose of Td, followed by one dose of either *Pac Merieux* or pa at least one month later.

Vaccine Administration: Intramuscular injection in the deltoid region of the left arm for dTpa, Infanrix®, and Td. Intramuscular injection in the deltoid region of the right arm for *Pac Merieux* and pa.

Concomitant Vaccines: Administration of any other vaccine by the parenteral route or of any other non-licensed vaccine was not permitted.

Study Visits: At the first visit, a physical examination was performed; pre-vaccination blood samples were collected; subjects received one dose of study vaccine; and diary cards for recording body temperature and adverse reactions were provided. At visit 2, (day 23 to 42 after vaccination), a physical examination was performed; post-vaccination blood samples were collected; and the diary card was collected. Subjects in the Td group received the assigned acellular pertussis vaccine at the second visit or at a third visit. Following receipt of the acellular pertussis vaccine, subjects in the Td group received diary cards for recording adverse reactions, and had a subsequent visit approximately one month later.

Safety Monitoring: Following vaccination, each subject was observed closely for 15 minutes. Diary cards were used by parents/guardians of subjects to record information on solicited adverse events occurring on the day of vaccination and for the subsequent 14 days. Information on unsolicited adverse events and serious adverse events was recorded through 30 days following vaccination.

Table 5. Study APV-118: solicited adverse events

Local	**General**
Pain on digital pressure at the injection site, including intensity[1]	Fever[2]
Redness, including diameter	Diarrhea, including intensity[1]
Swelling, including diameter	Irritability, including intensity[1]
	Loss of appetite, including intensity[1]
	Vomiting, including intensity[1]

[1] Intensity was graded as:
0 = none
1 = easily tolerated
2 = causing sufficient discomfort to interfere with daily activities
3 = prevented normal everyday activities and need medical advice
[2] Axillary temperatures were recorded daily. Temperatures $\geq$37.5^{o}C were considered fever. Temperatures >39.0 ^{o}C were considered grade 3 fever.

Written information provided to parents/guardians indicated that after a booster vaccination with Infanrix®, local reactions are expected in less than 10% of children and fever $\geq$39^{o}C occurs only rarely. Regarding extensive limb swelling, it was stated that occasionally, larger swelling of the limb has been reported following administration of Infanrix®, and that this swelling generally resolves over 4 days without lasting effects. The parents/guardians were instructed to contact the investigator immediately for any concerning signs/symptoms. For any reports of extensive swelling of the injected limb, the child was to be brought to the investigator's office for evaluation, at which time the study staff were to record the intensity of the swelling, the circumference of the injected and opposite limbs, the presence and extent of associated redness, pain, warmth, and the body temperature.

Statistical Considerations: Planned enrollment was a total of 440 subjects in order to obtain 400 evaluable subjects (220 to receive dTpa, 110 to receive Infanrix®, and 110 to receive Td). The sample size was based on the primary objective of comparing the immunogenicity of dTpa and Infanrix® for the pertussis antigens.

6.4 Safety Results

6.4.1 Enrolled subjects and reasons for elimination

The primary analysis of safety was performed on a modified intent to treat (ITT) cohort which included all enrolled subjects with safety data available who received Infanrix® for all 4 previous DTaP doses.

Table 6. Study APV-118: Number of subjects in the Infanrix® group and reason for elimination from the modified ITT cohort for safety, revised safety analysis

Number of subjects planned	110
Number of subjects enrolled	107
Elimination due to: -Fourth dose was not Infanrix® -Vaccine received for 4th dose not specified	 13 1
modified ITT cohort for safety	93

source: STN 103647/5001.5001, Volume 5, page 1300 and STN 103647/5001.5004, page 11

6.4.2 Demographic characteristics

Among subjects in the Infanrix® group who were included in the modified ITT cohort for safety, 50.5% were male, 98.9% were white, and the mean age at vaccination was 5.3 years.

6.4.3 Solicited adverse events

Table 7. Incidence of solicited adverse events with onset within 3 days (day 0, 1, or 2) following a fifth consecutive dose of Infanrix®, modified ITT cohort for safety (revised analysis)

Symptom	(N=93) n (%) [95% CI]
Pain	
any	60 (64.5) [53.9, 74.2]
grade 2[*] or 3[ı]	19 (20.4) [12.8, 30.1]
grade 3	1 (1.1) [0.0, 5.8]
Redness	
any	48 (51.6) [41.0, 62.1]
≥50 mm	22 (23.7) [15.5, 33.6]
≥110 mm	4 (4.3) [1.2, 10.6]
Swelling	
any	40 (43.0) [32.8, 53.7]
≥50 mm	14 (15.1) [8.5, 24.0]
≥110 mm	4 (4.3) [1.2, 10.6]
Fever[§]	
any	12 (12.9) [6.8, 21.5]
grade 3	0 (0.0) [0.0, 3.9]
Diarrhea, any	4 (4.3) [1.2, 10.6]
Irritability, any	17 (18.3) [11.0, 27.6]
Loss of appetite, any	13 (14.0) [7.7, 22.7]
Vomiting, any	0 (0.0) [0.0, 3.9]

[*] grade 2 = causing sufficient discomfort to interfere with daily activities

[ı] grade 3 = prevented normal everyday activities and need medical advice

[§] any = axillary/oral temperature ≥37.5°C, rectal ≥38.0°C; grade 3 = axillary/oral temperature ≥39.1°C, rectal ≥39.6°C

source: STN 103647/5001.5003, page 7

Among subjects who received Infanrix®, all solicited local symptoms had an onset on days 0, 1, or 2 following vaccination. For one case of pain and one case of redness, the intensity increased to grade 3 or ≥50 mm, respectively, beyond this period.

6.4.4 Unsolicited adverse events

6.4.4.1 Extensive swelling of the injected limb

In the modified ITT cohort, 9 of 93 subjects (9.7%) who received a fifth consecutive dose of Infanrix® spontaneously reported extensive swelling of the injected limb. The reported frequency of extensive swelling was 3.8% among dTpa recipients and 4.9% among Td recipients. Among the nine subjects in the Infanrix® group who reported extensive swelling of the injected limb, the mean diameter of the maximum local swelling reported during the 15-day follow-up period was 119.3 mm (4.8 inches), range (23-250 mm; 0.9-10 inches). The mean increase in the circumference of the injected arm was 4.4 cm (1.8 inches), range (2-7 cm; 0.8-2.8 inches) [this information was not available for one case]. In all cases, the swelling had an onset within the first three days following vaccination (i.e., on Day 0, 1, or 2). The median duration of swelling was 4 days (range 2-5 days). Intensity was regarded as grade 1 (easily tolerated) in three cases, grade 2 (interfered with daily activities) in four cases, and grade 3 (prevented normal activities and needed medical advice) in two cases. All cases of extensive swelling were associated with pain, redness, and warmth; one was associated with fever. Among cases of extensive swelling in the *Infanrix* group, one was further described as involving the chest and two were noted to involve the entire upper arm from the shoulder to the elbow.

6.4.4.2 Serious adverse events

No serious adverse events were reported in subjects who received Infanrix®. [One subject underwent adenoidectomy 29 days after dTpa; one subject sustained a burn to the hand 24 days after Td and underwent skin grafting].

6.4.5 Occurrence of local adverse events following a fifth dose of Infanrix® in relation to local adverse events after previous doses

Among subjects in the Infanrix® group, 85 had available data on adverse events following the first four doses of Infanrix®. To explore whether subjects with local adverse events after previous doses were at risk for severe local adverse events after the fifth dose, these 85 subjects were included in the analyses presented in Tables 8-10.

Table 8. Frequency of spontaneously reported extensive swelling following the fifth consecutive dose of Infanrix®, according to presence of solicited swelling following any previous dose of Infanrix®, subjects in Study APV-118 with available data for doses 1-4

Doses 1-3 in Study APV-039; dose 4 in Study APV-039B	N	Fifth dose in Study APV-118 Spontaneously reported extensive swelling of injected limb n (%)
Severe swelling after any of doses 1-4	7	2 (28.6)
Mild or moderate swelling after any of doses 1-4	25	1 (4.0)
No swelling after any of doses 1-4	53	6 (11.3)

source: STN 103647/5001.5001, Volume 5, page 1306

Table 9. Frequency of severe solicited swelling following the fifth consecutive dose of Infanrix®, according to presence of solicited swelling following any previous dose of Infanrix®, subjects in Study APV-118 with available data for doses 1-4

Doses 1-3 in Study APV-039; dose 4 in Study APV-039B	N	Fifth dose in Study APV-118 severe solicited swelling n (%)
Severe swelling after any of doses 1-4	7	3 (42.9)
Mild or moderate swelling after any of doses 1-4	25	5 (20.0)
No swelling after any of doses 1-4	53	6 (11.3)

source: STN 103647/5001.5001, Volume 5, page 1307

Table 10. Frequency of severe solicited redness following the fifth consecutive dose of Infanrix®, according to presence of solicited redness following any previous dose of Infanrix®, subjects in Study APV-118 with available data for doses 1-4

Doses 1-3 in Study APV-039; dose 4 in Study APV-039B	N	Fifth dose in Study APV-118 severe solicited redness n (%)
Severe redness after any of doses 1-4	9	3 (33.3)
Mild or moderate redness after any of doses 1-4	29	9 (31.0)
No redness after any of doses 1-4	47	11 (23.4)

source: STN 103647/5001.5001, Volume 5, page 1308

6.4.6 Comparative analyses of solicited local adverse events

Analyses comparing the frequency of local reactions across vaccine groups were performed on the according to protocol (ATP) cohort for reactogenicity that included all subjects who had received at least one dose of study vaccine according to their random assignment, with sufficient data to perform an analysis of safety, and who had not received a vaccine not specified or forbidden in the protocol. These results are presented in Tables 11 and 12.

Table 11. Incidence of solicited local adverse events with onset within 3 days (day 0, 1, or 2) and within 15 days following vaccination, ATP cohort for reactogenicity (revised analysis)

		Infanrix® N = 87	dTpa N = 177	Td N = 85
Symptom	Onset	n (%) [95% CI]	n (%) [95% CI]	n (%) [95% CI]
Pain				
any	3 days	55 (63.2) [52.2, 73.3]	86 (48.6) [41.0, 56.2]	45 (52.9) [41.8, 63.9]
	15 days	55 (63.2) [52.2, 73.3]	86 (48.6) [41.0, 56.2]	45 (52.9) [41.8, 63.9]
grade 3*	3 days	1 (1.1) [0.0, 6.2]	2 (1.1) [0.1, 4.0]	2 (2.4) [0.3, 8.2]
	15 days	2 (2.3) [0.3, 8.1]	2 (1.1) [0.1, 4.0]	2 (2.4) [0.3, 8.2]
Redness				
any	3 days	43 (49.4) [38.5, 60.4]	59 (33.3) [26.4, 40.8]	32 (37.6) [27.4, 48.8]
	15 days	43 (49.4) [38.5, 60.4]	60 (33.9) [27.0, 41.4]	32 (37.6) [27.4, 48.8]
≥50 mm	3 days	22 (25.3) [16.6, 35.7]	26 (14.7) [9.8, 20.8]	16 (18.8) [11.2, 28.8]
	15 days	23 (26.4) [17.6, 37.0]	27 (15.3) [10.3, 21.4]	16 (18.8) [11.2, 28.8]
Swelling				
any	3 days	37 (42.5) [32.0, 53.6]	56 (31.6) [24.9, 39.0]	30 (35.3) [25.2, 46.4]
	15 days	37 (42.5) [32.0, 53.6]	56 (31.6) [24.9, 39.0]	30 (35.3) [25.2, 46.4]
≥50 mm	3 days	14 (16.1) [9.1, 25.5]	23 (13.0) [8.4, 18.9]	12 (14.1) [7.5, 23.4]
	15 days	14 (16.1) [9.1, 25.5]	23 (13.0) [8.4, 18.9]	12 (14.1) [7.5, 23.4]

* grade 3 = prevented normal everyday activities and need medical advice
source: STN 103647/5001.5001, page 1302

Table 12. Differences between groups in the proportion of subjects with local solicited adverse events during the 15-day follow-up period, ATP cohort for reactogenicity (revised analysis)

	Difference in proportion of subjects		
Group	with any pain [90% CI]	with any redness [90% CI]	with any swelling [90% CI]
Infanrix® minus dTpa	14.6 [3.8, 26.4]	15.5 [4.6, 27.3]	10.9 [0.0, 22.6]
Td minus dTpa	4.4 [-6.7, 16.4]	3.7 [-7.0, 15.8]	3.7 [-7.0, 15.7]

source: STN 103647/5001.5001, page 1303

7.0 Study APV-120: Clinical study of the reactogenicity and immunogenicity of SKB's DTPa vaccine administered as a booster to healthy children 4 to 6 years of age, previously vaccinated with four doses of SKB's DTPa vaccine in the first two years of life.

7.1 Safety Objectives pertaining to Infanrix®
Primary: To evaluate the reactogenicity of the study vaccine.

7.2 Design: Open, uncontrolled study.

7.3 Protocol

Study Period: October 2, 1997 - September 8, 1998

Study population: The study was conducted at 16 sites in Germany.

Inclusion criteria

- vaccinated with four doses of Infanrix® in the first two years of life
- healthy child between 4 and 6 years of age
- written informed consent obtained from the parents/guardians

Exclusion criteria

- history of a fifth dose of diphtheria, tetanus and/or pertussis vaccine
- history of diphtheria, tetanus and/or pertussis disease
- history of allergic disease likely to be exacerbated by the vaccine
- major congenital defects or serious chronic illness
- history of progressive neurological disease
- immunosuppressive therapy (with the exception of topical corticosteroids)
- any suspected or confirmed immune disorder (including HIV infection)
- administration of immunoglobulins and/or any blood products within the three months preceding vaccination or during the study period
- acute febrile illness ($\geq$37.5^{o}C, axillary or oral) at time of planned vaccination
- use of any investigational or non-registered drug or vaccine during the study period or within 30 days prior to the start of the study
- simultaneous administration of a vaccine not foreseen by the study protocol during the study period or within 30 days prior to the start of the study
- absolute contraindications or precautions for an additional DTP vaccine dose:
    - hypersensitivity reaction to the vaccine
    - encephalopathy within 10 days of vaccination
    - fever $\geq$40.5^{o}C (rectal temperature; >40.0^{o}C axillary) within 48 hours of vaccination
    - collapse or shock like state (hypotonic hyporesponsive episode) within 48 hours of vaccination
    - seizures within 7 days of vaccination
    - persistent, inconsolable screaming or crying for $\geq$3 hours, within 48 hours of vaccination

Study Vaccine: Infanrix®

Vaccination Schedule: One dose of Infanrix®.

Vaccine Administration: Intramuscular injection in the deltoid region of the left arm.

Concomitant Vaccines: Administration of any other vaccine by the parenteral route was not permitted.

Study Visits: At the first visit, a physical examination was performed; parents were asked if they would allow their child to be bled, and only if they accepted, was the child bled; subjects received one dose of study vaccine; and diary cards for recording body temperature and adverse reactions were provided. At the second visit (on day 30-35 after vaccination), a physical examination was performed; post-vaccination blood samples were collected from subjects who were bled at the first visit; and the diary card was collected.

Safety Monitoring: Following vaccination, each subject was observed closely for 15 minutes. Diary cards were used by parents/guardians to record information on solicited adverse events occurring on the day of vaccination and for the subsequent 14 days.

Table 13. Study APV-120: Solicited adverse events

Local	**General**
Pain, including intensity[1]	Fever[2]
Redness, including diameter	Diarrhea , including intensity[1]
Swelling, including diameter	Irritability, including intensity[1]
	Loss of appetite, including intensity[1]
	Vomiting, including intensity[1]

[1]Intensity was graded as follows:
0 = none
1 = easily tolerated
2 = causing sufficient discomfort to interfere with daily activities
3 = prevented normal everyday activities and need medical advice
[2] Temperatures were recorded daily; axillary was the recommended route of measurement. Axillary/oral temperatures $\geq$37.5°C or rectal temperatures $\geq$38.0°C were considered fever. Axillary/oral temperatures $\geq$39.1°C or rectal temperatures $\geq$39.6°C were considered grade 3 fever.

Unsolicited and serious adverse events were to be recorded through 30 days post-vaccination.

In written information given to parents at the time of obtaining informed consent, it was stated that local reactions after a primary series occur in about 5-15% of children, and that these reactions are expected to occur more often after the booster vaccination. It was also stated that high fever $\geq$39° C is extremely rare. Regarding extensive limb swelling, it was stated that occasionally, larger swelling of the limb has been reported following administration of Infanrix®, and that this swelling generally resolves over 4 days without lasting effects. The parents/guardians were instructed to contact the investigator immediately for any concerning signs/symptoms. For any reports of extensive swelling of the injected limb, the child was to be brought in for evaluation, at which time the study staff were to record the intensity of the swelling, the circumference of the injected and opposite limbs, the presence and extent of associated redness, pain, warmth, and the body temperature.

Statistical Considerations: A sample size of 400 subjects provided 95% probability that the following adverse events occur at the specified frequencies in the study population:

Event	Expected frequency	Frequency in study population
Fever $\geq$38.9°C	4.6%	2.8% to 7.3%
Redness $\geq$ 20 mm	40.9%	36.1% to 45.9%
Swelling $\geq$ 20 mm	45.5%	40.6% to 50.5%
Severe pain	4.6%	2.8% to 7.3%

7.4 Safety Results

7.4.1 Enrolled subjects and reasons for elimination

The primary analysis of safety was performed on a modified intent to treat (ITT) cohort which included

all enrolled subjects with safety data available who received Infanrix® for all 4 previous DTaP doses and who did not report an underlying medical condition that could have interfered with safety assessments.

Table 14. Study APV-120: Number of subjects and reason for elimination, revised safety analysis

Number of subjects planned	440
Number of subjects enrolled	413
Elimination due to: -No safety data available -Fourth dose was not Infanrix® -Underlying chronic medical condition	 3 18 2
modified ITT cohort for safety	390

source: STN 103647/5001.5001, Volume 5, page 1318-1319 and STN 103647/5001.5004, page 11

7.4.2 Demographics

Among subjects in the modified ITT cohort for safety, 52.8% were male; the mean age at vaccination was 4.9 years, and 98.2% were white.

7.4.3 Solicited adverse events

Table 15. Study APV-120: Incidence of solicited general symptoms with onset within 3 days (day 0, 1, or 2) following vaccination, modified ITT cohort (revised analysis)

Symptom	N = 390 n (%) [95% CI]
Fever*	
any	44 (11.3) [8.3, 14.8]
grade 3	0 (0.0) [0.0, 0.9]
Diarrhea, any	15 (3.8) [2.2, 6.3]
Irritability, any	55 (14.1) [10.8, 18.0]
Loss of appetite, any	40 (10.3) [7.4, 13.7]
Vomiting, any	8 (2.1) [0.9, 4.0]

* any = axillary/oral temperature $\geq$37.5^{o}C, rectal $\geq$38.0^{o}C; grade 3 = axillary/oral temperature $\geq$39.1^{o}C, rectal $\geq$39.6^{o}C

source: STN 103647/5001.5004, page 13

Table 16. Study APV-120: Incidence of solicited local symptoms with onset during the 15-day follow-up period and during the first three days (days 0, 1, or 2) following vaccination, modified ITT cohort (revised safety database)

Symptom	Intensity	Onset	N = 390 n (%) [95% CI]
Pain	any	3 days	194 (49.7) [44.7, 54.8]
		Total	199 (51.0) [45.9, 56.1]
	grade 2 or 3	3 days	54 (13.8) [10.6, 17.7]
		Total	55 (14.1) [10.8, 18.0]
	grade 3	3 days	6 (1.5) [0.6, 3.3]
		Total	6 (1.5) [0.6, 3.3]
Redness	any	3 days	203 (52.1) [47.0, 57.1]
		Total	204 (52.3) [47.2, 57.4]
	≥ 5 cm	3 days	114 (29.2) [24.8, 34.0]
		Total	114 (29.2) [24.8, 34.0]
	≥ 11 cm	3 days	25 (6.4) [4.2, 9.3]
		Total	26 (6.7) [4.4, 9.6]
Swelling	any	3 days	193 (49.5) [44.4, 54.6]
		Total	197 (50.5) [45.5, 55.6]
	≥ 5 cm	3 days	78 (20.0) [16.1, 24.3]
		Total	80 (20.5) [16.6, 24.9]
	≥ 11 cm	3 days	20 (5.1) [3.2, 7.8]
		Total	20 (5.1) [3.2, 7.8]

source: STN 103647/5001.5004, page 14

7.4.4 Unsolicited adverse events

7.4.4.1 Extensive swelling of the injected limb

In the modified ITT cohort, 25 of 390 subjects (6.4%) who received a fifth consecutive dose of Infanrix® spontaneously reported extensive swelling of the injected limb. Among subjects who reported extensive swelling, the mean diameter of local swelling was 97 mm (3.9 inches), range (0-220 mm; 0-8.8 inches). Among 22 subjects with information on arm circumference, the mean increase in the circumference of the injected arm was 3.8 cm (1.5 inches), range (1.2-16 cm; 0.5-6.4 inches). In all cases, the swelling had an onset within three days of vaccination. The median duration of swelling was 4 days (range 1-10 days). Intensity was regarded as grade 1 (easily tolerated) in thirteen cases, grade 2 (interfered with daily activities) in eleven cases, and grade 3 (prevented everyday activities

and needed medical advice) in one case. All cases were associated with redness, 22 cases were associated with pain and 20 cases were associated with local warmth. The associated redness and warmth was usually diffuse (i.e., involving an area of the limb more extensive than the injection site). Three cases were associated with fever.

7.4.4.2 Serious adverse events

No serious adverse events were reported. One case of circulatory failure with onset on day 22, duration of 1 day, and grade 2 intensity, was reported. The subject recovered and the event was classified as not serious.

7.4.5 Occurrence of local adverse events following a fifth dose of Infanrix® in relation to local adverse events after previous doses

For 194 subjects, data were available data on solicited adverse events following the first four doses of Infanrix®. To explore whether subjects with local adverse events after previous doses were at risk for severe local adverse events after the fifth dose, these 194 subjects were included in the analyses presented in Tables 16-18.

Table 17. Frequency of spontaneously reported extensive swelling following the fifth consecutive dose of Infanrix®, according to presence of solicited swelling following any previous dose of Infanrix®, subjects in Study APV-120 with available data for doses 1-4

Doses 1-3 in Study APV-039; dose 4 in Study APV-039B	N	Fifth dose in Study APV-120 spontaneously reported extensive swelling of injected limb n (%)
Severe swelling after any of doses 1-4	8	0 (0)
Mild or moderate swelling after any of doses 1-4	43	4 (9.3)
No swelling after any of doses 1-4	143	8 (5.6)

source: STN 103647/5001.5001, Volume 5, page 1247

Table 18. Frequency of severe solicited swelling following the fifth consecutive dose of Infanrix®, according to presence of solicited swelling following any previous dose of Infanrix®, subjects in Study APV-120 with available data for doses 1-4

Doses 1-3 in Study APV-039; dose 4 in Study APV-039B	N	Fifth dose in Study APV-120 severe solicited swelling n (%)
Severe swelling after any of doses 1-4	8	2 (25.0)
Mild or moderate swelling after any of doses 1-4	43	8 (18.6)
No swelling after any of doses 1-4	143	32 (22.4)

source: STN 103647/5001.5001, Volume 5, page 1248

Table 19. Frequency of severe solicited redness following the fifth consecutive dose of Infanrix®, according to presence of solicited redness following any previous dose of Infanrix®, subjects in Study APV-120 with available data for doses 1-4

Doses 1-3 in Study APV-039; dose 4 in Study APV-039B	N	Fifth dose in Study APV-120 severe solicited redness n (%)
Severe redness after any of doses 1-4	13	5 (38.5)
Mild or moderate redness after any of doses 1-4	59	25 (42.4)
No redness after any of doses 1-4	122	35 (28.7)

source: STN 103647/5001.5001, Volume 5, page 1249

8.0 Reviewer's comments and conclusions

8.1 Safety of a fifth consecutive dose of Infanrix®

The safety of a fifth consecutive dose of Infanrix® has been studied in approximately 500 children ages 4-6 years of age. Available data demonstrate an increase in the frequency and severity of local reactions with successive doses (Table 20). The fourth and fifth dose studies shown in Table 20 may underestimate adverse events if subjects who experienced adverse events after previous doses were less likely to enroll in booster studies, and if such subjects are at higher risk for adverse events after booster doses. Unlike local adverse events, there were no apparent increases in systemic adverse events, including fever, following the fifth dose of Infanrix® compared with previous doses.

Table 20. Frequency (%) of solicited local adverse events occurring within the three days following vaccination with Infanrix® in German infants and children* in which all doses were Infanrix®.

	Study 039 N=2457			Study 039B N=1809	Study APV-118 N=93	Study APV-120 N=390
Event	Dose 1 (3 mo.)	Dose 2 (4 mo.)	Dose 3 (5 mo.)	Dose 4 (10-36 mo.)	Dose 5 (4-6 years)	
Redness						
any	8.9	23.6	26.6	45.9	51.6	52.1
> 2 cm	0	0.5	1.3	13.8	n/a	n/a
≥ 5 cm	n/a	n/a	n/a	n/a	23.7	29.2
≥ 11 cm	n/a	n/a	n/a	n/a	4.3	6.4
Swelling						
any	3.9	14.1	18.5	35.4	43.0	49.5
> 2 cm	0	0.3	1.3	11.4	n/a	n/a
≥ 5 cm	n/a	n/a	n/a	n/a	15.1	20.0
≥ 11 cm	n/a	n/a	n/a	n/a	4.3	5.1
Pain						
any	2.0	2.6	3.7	26.3	64.5	49.7
grade 2 or 3	n/a	n/a	n/a	n/a	20.4	13.8
grade 3	n/a	n/a	n/a	n/a	1.1	1.5

* Subjects who received Dose 4 are not necessarily a subset of subjects for whom data are available on doses 1-3; subjects who received dose 5 are not necessarily a subset of subjects for whom data are available for doses 1-3 or dose 4.

Data from studies 039 and 039B were derived from the current package insert for Infanrix®. Data from Study APV-118 were derived from STN 103647, December 19, 2002 FAX. Data from Study APV-120 were derived from STN 103647/5001.5004, page 14

n/a indicates data not available.

Since extensive swelling of the injected limb was not specifically solicited in studies of Infanrix®, the observed frequency of spontaneously reported cases may underestimate the true frequency. Data from Studies APV-118 and APV-120 indicate that these reactions are typically associated with an increase in limb circumference, pain, redness, and warmth, and often interfere with daily activities. The available data also indicate that these reactions generally resolve within approximately one week.

8.2 Severe or extensive local reactions after a fifth consecutive dose of Infanrix® relative to local reactogenicity after previous doses of Infanrix®

For Studies APV-118 and APV-120, descriptive exploratory analyses of the frequency of extensive or severe local adverse events following the fifth dose of Infanrix® were conducted, according to the occurrence and severity of local adverse events after previous doses of Infanrix®. These analyses were limited by relatively small numbers of subjects available who had local adverse events after the first four doses. Although no statistical analyses were performed, the data from Study APV-118 suggested a trend towards a higher frequency of unsolicited extensive swelling, severe solicited swelling, and severe solicited redness, with the occurrence of severe local adverse events following a previous dose of Infanrix®. The data from Study APV-120 revealed no obvious trends in the occurrence of extensive or severe local reactions following the fifth dose of Infanrix® relative to local reactogenicity following previous doses of Infanrix®. Based on the available data from these studies, it is difficult to draw conclusions as to whether subjects who experience local adverse events following the first four doses of Infanrix® may be at risk for extensive or severe local reactions following the fifth

dose.

8.3 Use of Infanrix® for the fourth or fifth dose following three or four doses of other DTaP vaccines.

One of the requested indications in this Supplement is for the use of Infanrix® for the fourth or fifth dose following three or four doses of any DTaP vaccine. However, no data were submitted to support this indication.

8.4 Reduced antigen content vaccine

Although the comparative safety analyses in Study APV-118 were secondary analyses, and criteria for making comparisons between groups were not pre-specified, the available data suggest that the reduced antigen content vaccine, dTpa, may be associated with fewer local adverse events, overall, than Infanrix®, when given as a fifth dose following four previous doses of Infanrix®. Review of the immunogenicity data from this study has been assigned to another reviewer. [----------
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9.0 Post-marketing evaluation of a fifth consecutive dose of Infanrix® or DTaP-IPV (Infanrix®-IPV) following four previous doses of Infanrix®

In order to estimate the frequency of and characterize extensive swelling reactions in U.S. children, GSK has agreed to submit to the Infanrix® IND the safety results of an ongoing study (Study 047) in which extensive local reactions are being actively monitored in children ages 4-6 years who receive a dose of Infanrix® ---------- four previous doses of Infanrix®. Study 047 was initiated in October 2002 under GSK's IND (----------) --
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---------- in healthy U.S. children 4 to 6 years of age who previously received 4 doses of Infanrix®. ----------
---------- Completion of the study is expected by October 2004. The sponsor has agreed to submit an interim study report on safety that will include follow-up of all subjects through one month post-vaccination, and a final safety report that will also include follow-up of all subjects through 6 months post-vaccination. The projected dates of submission of the interim safety report and the final safety report are July 2004 and January 2005, respectively.

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